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TITLE: Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound

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CONTRACTING ORGANIZATION: National Trauma Institute, San Antonio, TX 78230

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14. ABSTRACT
The Combat Casualty Care Research Program, through the JWMRP, is specifically interested in testing and refining techniques for early intervention in life-threatening battle injuries. The purpose of this study is to determine the utility of ultrasonic assessment protocol of inferior vena cava vena cava diameter and collapsibility to detect and aid in management of non-compressible hemorrhage in major trauma victims. During the second year of this project, remaining subcontracts to participating sites were issued, local Institutional Review Board and HRPO approval was received/continued and all research staff and clinician sonographers were recruited and trained. The University of Maryland replaced Emory University as the fourth clinical site. All four clinical sites screened and enrolled patients. During year 2, 851 patients were screened and 66 were enrolled. A modification for a 12-month no cost extension was executed on September 12, 2017 to allow more time for subject accrual and data analyses. There are no major finding or results at this time.

15. SUBJECT TERMS
Trauma; hypovolemia; inferior vena cava; IVC; internal jugular; IJ; collapsibility; injury; ultrasound; hemorrhagic shock

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Introduction:
The National Trauma Institute (NTI) proposed to utilize $ 498,269 in Joint Warfighter Medical Research Program Funding to extend the work previously completed at academic trauma centers using bedside ultrasound to identify patients with evidence of hypovolemia as determined by inferior vena cava (IVC) and internal jugular (IJ) collapsibility. Prior small studies of ultrasonographic assessment of IVC and IJ diameters and collapsibility demonstrated it to be a sensitive detector of blood volume loss and hemorrhagic shock. The specific aims of this study are: (1) determine the sensitivity, specificity and accuracy of ultrasonic assessment (USA) of IVC diameters in detecting traumatic shock at admission as compared to vital signs, (2) determine the ability of USA of IVC diameters to detect preclinical shock states defined by elevated arterial blood gas (ABG) Base Deficit or lactate in trauma patients without hypotension (SBP less than 90) at admission, (3) correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU, such as correction of Base Deficit or lactate, evidence of improved organ perfusion such as urine output, limited echocardiography and avoidance of multiple organ dysfunction or death. The initial four clinical sites for this study are University of California at San Diego (UCSD), Virginia Commonwealth University (VCU), University of Utah (Utah), and Emory University at Grady Memorial Hospital (Emory). In Year 2 Quarter 2, Emory University was replaced as a site by the University of Maryland (UMD).

Keywords:
Trauma; hypovolemia; inferior vena cava; IVC; internal jugular; IJ; collapsibility; injury; ultrasound

Accomplishments:
The major goals of this project as identified in the Statement of Work are below with percent completion determinations and completion dates as appropriate.

Aims and Major Goals	**Timeline in Months**	**Actual completion date**	**% of completion**
Specific Aim 1: Prepare for Clinical Trial			
If Applicable, coordinate with Sites for CRADA* submission	1-3	N/A	N/A
If Applicable, coordinate with Sites for material transfer agreements (MTAs) or clinical trial agreements (CTAs) submission	1-3	N/A	N/A
Refine eligibility criteria, exclusion criteria, screening protocol	1-3	17/09/2015	100%
Finalize consent form & human subjects protocol	1-3	17/09/2015	100%
Coordinate with Sites for IRB** protocol submission	1-3	01/10/2015	100%
Coordinate with Sites for UCSD IRB review	1-6	06/07/2016	100%
Start-up activities	1-6	14/06/2017	100%
Coordinate with Sites for Military 2nd level IRB** review (ORP/HRPO)	1-6	06/04/2017	100%

Submit amendments, adverse events and protocol deviations as needed	As Needed		0%
Coordinate with Sites for annual IRB** report for continuing review	Annually		66%
*Milestone Achieved: Local IRB** approval at VCU, Utah and Emory*	1-6	19/01/2017	100%
*Milestone Achieved: HRPO*** approval for all protocols*	6	06/04/2017	100%
*Milestone Achieved: local IRB** approval for all protocols through UCSD.*	6	06/07/2016	100%
Specific Aim 2: Coordinate Study Staff for Clinical Trial			
Sites identify or hire SRAs, Train clinician sonographers	3-6	03/05/2017	100%
Milestone Achieved: Research staff trained	3-6	02/09/2017	100%
Specific Aim 3: Randomized Controlled Trial - Conduct Study, Report Findings			
(1) determine the sensitivity, specificity and accuracy of ultrasonic assessment (USA) of IVC diameters in detecting traumatic shock at admission as compared to vital signs, (2) determine the ability of USA of IVC diameters to detect preclinical shock states defined by elevated arterial blood gas (ABG) Base Deficit or lactate in trauma patients without hypotension (SBP less than 90) at admission, (3) correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU, such as correction of Base Deficit or lactate, evidence of improved organ perfusion such as urine output, limited echocardiography and avoidance of multiple organ dysfunction or death.	6-24		15%
Demonstrate equivalency of pocket ultrasound devices for IVC exam	12-18		0%
Milestone Achieved: 1st participant consented, screened and enrolled in study	6	29/07/2016	100%

During this reporting period, all four sites received IRB and HRPO approval, all study staff were trained and enrolling subjects. The National Trauma Institute (NTI) received a12-month no cost extension (new end date of 14-09-2018). During year 2, a total of 851 patients were screened and 66 were enrolled in the study. To date (since study initiation), UCSD has screened 239 subjects and enrolled 33 subjects. VCU has screened 39 and enrolled 9 subjects, Utah has screened 150 subjects and enrolled 4 subjects, and UMD has screened 528 and enrolled 28 subjects (total screened = 956; total enrolled = 74). Training of research staff and sonographers has been completed at all sites which included research ethics, consent procedures, and IVC and IJ ultrasound examinations.

UCSD, VCU, Utah, and Emory were the initial sites for this project. However, Emory withdrew from the project (08 Aug 2016) due to internal research infrastructure limitations. UMD who was a participating site under the earlier project, agreed to reopen the study to participate as the fourth site. A request for a modification of the Statement of Work for the site change was submitted and approved during the second quarter of Year 2.

With respect to training opportunities associated with this study, Dr. Doucet has produced “Protocol Video USA-IVC Study (Version 5)” that is posted on youtube: https://youtu.be/54-Z6fiJpPY This video describes study design and procedures, inclusion/exclusion criteria and includes a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants.

At this stage of the project, there are no results to disseminate to communities of interest. Plans for the next quarterly reporting period include continued enrollment, and initial data analysis. Dr. Doucet will present a study update to the NTI Board of Directors on September 30, 2017.

Impact:
At this stage of the project, there has been no impact on the principal discipline, other disciplines, technology transfer, or society beyond science and technology**.**

Changes/Problems:
The NTI Director of Research (Michelle Price) discussed low subject accrual with Dr. Doucet in August 2017. The lower accrual rate is due to less subjects being eligible for enrollment at screening. Based on preliminary data analysis, Dr. Doucet anticipates a lower sample size will be required to achieve study aims and objectives. He estimates that a sample of approximately 125 study subjects will be sufficient to produce clinically significant results. At the current accrual rate, 125 subjects should be enrolled by March 2018. These data will be analyzed and submitted in Spring 2018 for presentation at professional conferences in Fall 2018. USAMRMC approved a 12-month no cost extension for these activities.

Products:
Dr. Doucet has produced “Protocol Video USA-IVC Study (Version 5) that is posted on youtube: https://youtu.be/54-Z6fiJpPY This video contains study design, procedures, inclusion/exclusion criteria and a demonstration to train clinical sonographers on correct techniques to measure IVC diameter in research participants. This video is used for ongoing training.

Participants & Other Collaborating Organizations:

Participants

Name	Project Role	Nearest person month worked	% Effort	Contribution to the project
Donald Jenkins	Principal Investigator	1	5%	Oversight of entire project
Michelle Price	Program Manager	1	2.5%	Regulatory oversight and coordination of regulatory reviews and reporting
Amy Flores	Controller	1	5%	Managed Subaward
Pam Bixby	Knowledge Translation	1	2.5%	Managed dissemination of findings

Starting 01/10/2016, Michelle Price replaced Roy Estrada as Program Manager, and beginning 01/11/2016 Amy Flores replaced Monica Phillips as Controller. The table above provides all current information for project staff.

The other support information has changed for PI, Donald Jenkins, MD. The project previously listed under current that was titled “A National Coordinating Center for Trauma Research Funding” (W81XWH-11-1-0841) has ended, and Dr. Jenkins currently has effort on three projects. The first project is titled “A National Coordinating Center for Trauma Research” (W81XWH-15-2-0089), and the following two projects "A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood" (W81XWH-15-2-0039) and “Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound” (W81XSH-15-1-0709) were previously under pending and are now funded projects. There is no overlap between funded support and dates. The most current information for other support is included in the appendix.

Other Collaborating Organizations

Organization	Location	Contribution to Project
University of California San Diego	200 W Arbor Drive, #8896, San Diego, CA 92103	Lead clinical site, protocol design, data analyses (PI: Jay Doucet, MD)
Virginia Commonwealth University	1200 Broad Street, Richmond VA 23298	Clinical site (PI: Paula Ferrada, MD)
University of Utah	30 North 1900 East, 3B110, Salt Lake City, UT 84132	Clinical site (PI: Ram Nirula, MD)
University of Maryland	620 West Lexington Street, Room 5124, Baltimore, MD 21201-1531	Clinical Site (PI: Sarah, Murthi, MD)

Special Reporting Requirements:
The Quad Chart for this project follows.

Detection and Management of Non-Compressible Hemorrhage by Vena Cava Ultrasonography (USA-IVC)

ERMS/Log Number: JW140026
Award Number: W81XWH-15-2-0039

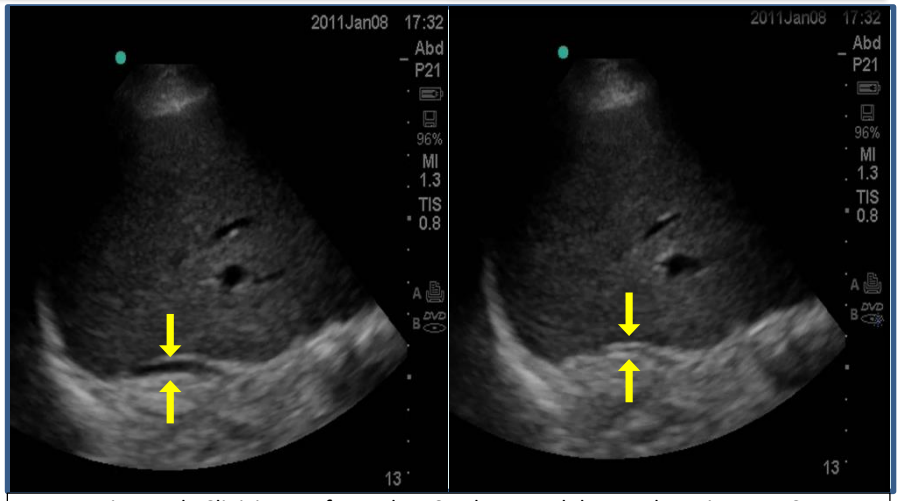
Grant PI: Donald Jenkins **PI:** Jay Doucet **Org:** NTI/UCSD **Award Amount:** $498,269

Study

1. Determine if ultrasonic assessment (USA) of Inferior Vena Cava (IVC) or Internal Jugular Vein (IJ) diameters is sensitive and specific in detecting hypovolemia at admission by predicting transfusion requirements.
2. Correlate the restoration of IVC diameters and collapsibility to achievement of endpoints of shock resuscitation in the ICU phase at 8-24 hours.

Approach

This is a randomized prospective clinical trial performed at 4 academic Level I trauma centers. Major trauma patients undergo a FAST abdominal ultrasound with USA of the IVC at admission and after minutes resuscitation. Patients with continued IVC collapse at the 2nd exam are considered Non-Responders to resuscitation. Their need for interventions and outcomes is compared to those with collapsible IVCs at admission that respond to initial resuscitation.



In our prior work, Clinician-performed FAST ultrasound detected persistent IVC Collapsibility in Major Trauma Victims which predicted 24 hour ongoing intravenous fluid requirements

Timeline

Activities CY	16	17
Patient Enrollment		
Develop standardized technique and training for USA-IVC exam		
Promulgate USA-IVC technique		

Updated: 10/10/17

Goals/Milestones:

CY16-17 Goal – Patient Enrollment
☑Start patient enrollment at 4 Level I Trauma Centers
CY17 Goal – Data Analysis
☐ Analyze data and disseminate findings via NTI meeting, abstract and peer review publication
CY17 Goal – Promulgate USA-IVC technique
☐ Develop learning tool kit to allow providers to learn USA-IVC technique and QA process, including for pocket sized ultrasound devices.

Previous, Current and Pending Support

Donald Jenkins, MD

Previous

Title: National Trauma Institute: A National Coordinating Center for Trauma Research Funding Funded by Department of Army. (W81XWH-11-1-0841). Contracting Officer: Elena Howell, 301-619-6871
Period of Performance: 9/29/11-9/28/16
Role: Principal Investigator, 5% (no salary report received)
Amount: $3,845,000.00
Brief Description: NTI will manage multiple studies of scientific merit in trauma and emergency or critical care medicine selected by peer-review. The clinical data resulting from these studies becomes a fundamental piece of infrastructure and a vehicle to knowledge. Both the initial set of studies funded through this contract, as well as potential new studies, will be used to establish a set of common data elements. Initially this would be a small but scalable data repository for both animal and human study data, giving trauma investigators access to more data than they are able to collect on their own, and providing a much faster route to the large datasets required to draw conclusions to improve trauma care.

Title: Microvesicle production after trauma & its Clinical Impact on Venothromboembolism. Funded by Department of Army. (W81XWH-10-2-0110).
Period of Performance: 10/2010-12/2015
Role: Co-Investigator, 5%
Amount: $1.5million
Brief Description: The major goals of this project are to fund the proposed prospective case-cohort study examining the role of microvesicle production and thrombin generation in those trauma patients who develop venothromboembolism.

Current:

Title: A National Coordinating Center for Trauma Research
Funded by: Department of Defense W81XWH-15-2-0089
Role: Principal Investigator, 5% effort
Amount: $199,997
Period of Performance: September 30, 2015 – September 29, 2018
Brief Description: The civilian trauma research community can be used as a surrogate for military combat casualty care research, maximizing the return from dollars invested by replacing the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research. As available research funding shrinks and federal budget pressure increases, we must replace the expensive and repetitive assembly and disassembly of short-lived clinical investigator networks with a stable and enduring operational infrastructure for clinical trauma research. This research effort funds two clinical studies, one simulation development, and the development of tools for the collection and dissemination of results and data from studies – the National Trauma Research Repository.
Specific Aims: 1. To manage specific research projects to address military research gaps; 2. To develop tools to allow for the collection and dissemination of results and data from studies.
No overlap

Title: A National Coordinating Center for Prehospital Trauma Research Funding Transfusion Using Stored Fresh Whole Blood
Funded by: Department of Defense. W81XWH-15-2-0039
Role: PI
Effort: 5%, no support
Amount: $499,995
Period of Performance: August 25, 2015 – August 24, 2018
Brief Description: This research effort funds a feasibility study examining a system for collection, banking, and delivery of FWB in a civilian trauma center and comparing the use of FWB leukocyte reduced with a platelet sparing filter to component therapy for trauma patients with hemorrhagic shock.
Specific Aims: (1) Determine the shelf life of whole blood units leukocyte reduced with a platelet sparing filter stored at 4 degrees. (2) Prospectively determine the effectiveness of whole blood leukocyte reduced with a platelet sparing filter compared to component therapy as measured by coagulation capacity after transfusion and clinical outcomes. (3) Determine the feasibility of providing an inventory of whole blood leukoreduced with a platelet sparing filter for resuscitation of trauma patients in hemorrhagic shock.
Overlap?: No

Title: Management of Noncompressible Hemorrhage Using Vena Cava Ultrasound
Funded by: Department of Defense. W81XSH-15-1-0709
Role: PI
Effort: 5%, no support
Amount: $498,269
Period of Performance: September 15, 2015 – September 14, 2018
Brief Description: The hypothesis of this research effort is that an ultrasonic assessment (USA) protocol of inferior vena cava (IVC) or internal jugular vein diameter and collapsibility can detect and aid management of non-compressible hemorrhage in major trauma victims.
Specific Aims: 1) Determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ultrasonic assessment (USA) of inferior vena cava expiration (IVCe), inferior vena cava inspiration (IVCi) and inferior vena cava collapsibility index (IVC-CI) or internal jugular expiration and inspiration (IJe, IJi) and internal jugular vein collapsibility index (IJ-CI) to predict the need for blood transfusion or hemostatic interventions such as surgery or angioembolization. 2) Determine the sensitivity, specificity and accuracy of USA of IVCe, IVCi and IVC-CI or IJe, IJi and IJ-CI with the classic clinical parameters for hypotension (SBP<90), indicative of hemorrhagic shock.
Overlap?: No

Pending:

Title: Development and Implementation of viable cold stored blood products on the Prehospital Resuscitation in severely injured patients in South Texas
Funds: South Texas Regional Advisory Committee/ San Antonio Area Medical Foundation
Project Rol: Co-PI
Effort: 1%, no salary support
Amount: $200,000
Period of performance: Pending
Brief Description: This award primary goal is to develop a functional cold stored whole blood product and implement a sustainable prehospital transfusion program for trauma patients in South Texas.

Title: Predictors of Venous Thromboembolism: A Multicenter Prospective Cohort Study
Funds: DOD/Mayo Clinic
Project Role: Co-PI
Effort: 5%
Amount: $303,317
Period of performance: Pending
Brief Description: To assess an individual patient's coagulation phenotype, using the Calibrated Automated Thrombinogram (**CAT**) to quantify the kinetics of plasma thrombin generation. In addition to testing the plasma coagulome by CAT, study directly address the Surgeon General's charge to "*conduct research into when genetic testing is appropriate*," by testing prothrombotic single nucleotide polymorphisms (**SNP**s) as risk factors for VTE among trauma patients. Study propose to validate a personalized and individualized VTE risk score for acutely injured patients and to address the NIH initiative of defining the *"role of laboratory monitoring… to help better define those at risk of bleeding and thrombosis*."

Title: Precision Medicine-based hemorrhage resuscitation utilizing individualized measurements of Anemia and Hypovolemia
Funds: NIH/Mayo Clinic
Project Role: PI
Effort: 5%
Amount: $61,020
Period of performance: Pending
Brief Description: To determine the ability for compensatory reserve index (CRM) to provide early and accurate resuscitation volume estimates in individual patients with varying compensatory responses compared to traditional vital sign measurements in hemorrhaging trauma patients. To develop and validate a clinically useful interface device (PROTOTYPE) that aggregates the CRM output and the modified-SpHb (percutaneous continuous hemoglobin monitor) mathematical model and directs blood product and fluid resuscitation in hemorrhaging trauma patients.